Acute myocardial injury is common in patients with covid-19 and impairs their prognosis

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ABSTRACT
Objective We sought to explore the prevalence and immediate clinical implications of acute myocardial injury in a cohort of patients with covid-19 in a region of China where medical resources are less stressed than in Wuhan (the epicentre of the pandemic).

Methods We prospectively assessed the medical records, laboratory results, chest CT images and use of medication in a cohort of patients presenting to two designated covid-19 treatment centres in Sichuan, China. Outcomes of interest included death, admission to an intensive care unit (ICU), need for mechanical ventilation, treatment with vasoactive agents and classification of disease severity. Acute myocardial injury was defined by a value of high-sensitivity troponin T (hs-TnT) greater than the normal upper limit.

Results A total of 101 cases were enrolled from January to 10 March 2020 (average age 49 years, IQR 34–62 years). Acute myocardial injury was present in 15.8% of patients, nearly half of whom had a hs-TnT value fivefold greater than the normal upper limit. Patients with acute myocardial injury were older, with a higher prevalence of pre-existing cardiovascular disease and more likely to require ICU admission (62.5% vs 24.7%, p=0.003), mechanical ventilation (43.5% vs 4.7%, p<0.001) and treatment with vasoactive agents (31.2% vs 0%, p<0.001). Log hs-TnT was associated with disease severity (OR 6.63, 95% CI 2.24 to 19.65), and all of the three deaths occurred in patients with acute myocardial injury.

Conclusion Acute myocardial injury is common in patients with covid-19 and is associated with adverse prognosis.

INTRODUCTION
The recent outbreak of covid-19 is a public health emergency of international concern and continues to spread worldwide. Knowledge concerning this threatening disease is accumulating rapidly, but many uncertainties remain, including detailed understanding of its extrapulmonary manifestations.

ACE2 has been identified as a functional receptor for coronaviruses and is highly expressed in the lungs as well as the heart.1 Electrocardiographic changes, troponin elevation and subclinical left ventricular diastolic impairment have been previously reported in patients with severe acute respiratory syndrome (SARS).2 3 Similarly, acute myocardial injury (defined by elevated levels of cardiac biomarkers, troponin or creatine kinase (CK)) appears to be frequent during the current outbreak of covid-19,4 although the mechanisms of injury and its clinical implications remain poorly defined. The majority of patients currently requiring hospital care for covid-19 are categorised as non-severe.5 It is therefore important to understand whether accompanying acute myocardial injury is a bystander phenomenon or an important contributor to immediate and long-term outcome with implications for clinical management.

Although recent reports have demonstrated the association of cardiac injury with mortality, these data arose from Wuhan, where medical resources have been most stressed,6 7 potentially augmenting the effect of cardiac injury due to delayed hospital admission and specialist management. Analysis of data from less stressed regions is also needed to confirm the broader significance of cardiac injury in covid-19. Accordingly, we sought to characterise the prevalence and clinical implications of acute myocardial injury in a large cohort of patients with laboratory-confirmed covid-19 in a region where clinical resources are under less pressure.

METHODS
Study population
We collected the data of 103 consecutive patients with laboratory-confirmed SARS-CoV-2 infection admitted to the Public Health Clinical Centre of Chengdu and West China Hospital, Sichuan University, between 16 January and 10 March 2020. Both institutions are certified covid-19 tertiary care hospitals and designated hub centres within Sichuan province. Laboratory-confirmed cases were defined by a positive result on high-throughput sequencing or real-time reverse-transcriptase–PCR assay of nasal and/or pharyngeal swabs.8

Data collection
Medical records, use of medications and the findings of laboratory investigations, chest CT and transthoracic echocardiography (TTE), where available, were collected from all patients. Admission laboratory investigations included full blood count, biochemical analysis, coagulation testing,
liver and renal function, inflammatory markers (C reactive protein (CRP) and procalcitonin (PCT)) and cardiac biomarkers (high-sensitivity troponin T (hs-TnT), creatine kinase and MB subfraction (CK-MB), N-terminal-proB-type natriuretic peptide (NT-proBNP) and lactate dehydrogenase (LDH)). TTE was performed if needed to guide clinical care, and all chest CT scans were evaluated by investigators blinded to patients’ clinical status.

Study outcomes
Key outcomes included disease severity (see further), admission to an intensive care unit (ICU), need for mechanical ventilation or vasoactive agents, and death.

Patient and public involvement
Patients and the public were not involved in the study design, analysis, interpretation and writing of the study.

Study definitions
Severity of covid-19 was classified at the time of admission using the novel coronavirus pneumonia diagnostic criteria and treatment regimens defined by the National Health Commission of the People’s Republic of China, and reclassified at the time of hospital discharge according to clinical evolution of the disease. These diagnostic criteria and treatment regimen have been recently updated to a seventh version, but criteria defining severe/critical case remain unchanged from the fourth version (published before discharge of the first case in this cohort). Severe (respiratory rate, ≥30 breaths/min; resting oxygen saturation, ≤93%; or $\text{PaO}_2/\text{FiO}_2$ ratio, ie, oxygenation index, ≤300 mm Hg) and critical (respiratory failure requiring mechanical ventilation, shock or need for intensive care) cases were grouped together for the purposes of this study. Acute myocardial injury was defined by an hs-TnT value greater than the institutional upper limit of normal (14 pg/mL). A single radiologist assessed the CT pulmonary lesion ratio (defined by the ratio of the sum of lesion areas on each slice to the total pulmonary tissue area) for all patients.

Statistical analysis
Continuous variables are expressed as medians (IQRs). Categorical variables are expressed as frequencies (percentages). Continuous variables were compared using the Student t-test or the Mann-Whitney U test, as appropriate, and categorical variables using $\chi^2$ test or the Fisher exact test, as appropriate. Since values of NT-proBNP and hs-TnT were not normally distributed, data were log-transformed for multivariate analyses. Pearson’s correlation was used to test the association between ejection fraction and log hs-TnT. A multivariate linear regression analysis was carried out to explore independent factors associated with hs-TnT levels. Those with $p<0.05$ in univariate analysis were introduced into the multivariate linear regression model. To investigate the impact of factors on disease severity, logistic regression analyses were carried out to determine ORs and 95% CIs for covariates with severe/critical disease as the bivariate outcome. Considering the number of events, we did not further perform multivariate logistic regression. We considered age and gender, daily habit, comorbidities, use of medications, lab tests and pulmonary issues for candidate variables in both regression models, which were age and gender, smoking, use of ACE inhibitor (ACEi), angiotensin II receptor blocker (ARB) or calcium channel blocker (CCB), estimated glomerular filtration rate (eGFR), CRP, white blood cell count (WBC), log NT-proBNP, log hs-TnT, pulmonary lesion ratio, oxygenation index and pre-existing coronary artery disease, hypertension, diabetes mellitus or cerebrovascular disease. All statistical analyses were performed using STATA/MP V.16.0, and a two-sided p value of <0.05 was considered statistically significant.

RESULTS
Two patients were excluded from analysis due to missing data. Among 101 patients (average age 49 years, IQR 34–62 years) with complete datasets, 16 (15.8%) had evidence of acute myocardial injury (hs-TnT>14 pg/mL) (figure 1). Baseline characteristics of patients with and without acute myocardial injury are displayed in table 1. Patients with cardiac injury were older, with a higher prevalence of pre-existing cardiovascular disease (hypertension, coronary artery disease and cerebrovascular disease), presented with more significant dyspnoea and were more frequently treated with ACEi, ARB and CCB. They also had lower eGFR and oxygenation index, higher CRP, PCT, NT-proBNP and other cardiac biomarkers (CK, CK-MB and LDH), and a greater pulmonary lesion ratio.

Univariate linear regression analyses using hs-TnT as a continuous variable demonstrated that age, use of ACEi or ARB, CRP, log NT-proBNP and pulmonary lesion ratio correlated positively with log hs-TnT (and inverse correlation with eGFR and oxygenation index) (table 2). In multivariate analysis, log hs-TnT was independently associated with the use of ACEi/ARB ($\beta=1.11, p<0.02$) and eGFR ($\beta=-0.017, p=0.006$). Among patients with TTE data (n=32), there was a negative correlation between ejection fraction and log TnT-hs ($r=-0.64, p<0.001$; figure 2).

Clinical outcomes were summarised in table 3. Patients with acute myocardial injury were more frequently classified as severe/critical (75.0% vs 29.4%, $p=0.001$) and were more likely to require admission to ICU (62.5% vs 24.7%, $p=0.003$), mechanical ventilation (43.5% vs 4.7%, $p<0.001$) and vasoactive agents (31.2% vs 0%, $p<0.001$). Furthermore, all of the three deaths occurred in patients with acute myocardial injury. Older age, hypertension, cerebrovascular disease, the use of CCB, lower eGFR, and elevated NT-proBNP hs-TnT...
and CRP were predictors of severe disease in the univariate analysis (table 4). All cases with the history of coronary artery disease were classified as severe cases.

**DISCUSSION**

Our study provides structured information concerning the role of acute myocardial injury in the setting of covid-19 in regions affected by the pandemic but where resources are less stressed. We demonstrate that elderly patients with pre-existing cardiovascular disease and using antihypertensive drugs (including ACEi and ARB) are more likely to present with acute myocardial injury, although with a lower incidence than those in Wuhan, the epicentre of the pandemic (15.8% vs 19.7%–27.8%), which in turn leads to more severe disease manifestations, including increased need for
Ventricular diastolic impairment in SARS,3 suggesting that it may be also frequent in non-severe cases. Given that the majority of cases are non-severe, clear management strategies for this subgroup of patients are of vital importance, particularly as covid-19 spreads worldwide. Our analysis demonstrates that acute myocardial injury complicating covid-19 infection (indicated by troponin elevation) is associated with a considerable disease burden, including classification as a severe/critical case, increased need for mechanical ventilation and use of vasoactive agents, and a higher risk of death.

Cardiac injury in itself may reflect an ongoing pathological insult due to cytokine release or secondary hypoxaemia.4 Conversely, a florid systemic inflammatory response or immune paresis in patients with cardiac injury is likely to be associated with more severe pulmonary manifestations. This hypothesis is partly supported by our observation that patients with acute myocardial injury also demonstrated higher levels of CRP and PCT and a greater pulmonary lesion ratio.

Patients with acute myocardial injury were generally the elderly, with a higher likelihood of pre-existing cardiovascular comorbidities and use of antihypertensive drugs, such as ACEi and ARB. Age and comorbidities are consistently identified as risk factors for adverse events in outbreaks of respiratory virus infection. Indeed, the severity of the primary respiratory syndrome and risk of adverse outcomes in Middle East respiratory syndrome was increased in patients with pre-existing cardiovascular disease.17 Mortality data from 44,672 cases of covid-19 released by the Chinese Centre for Disease Control and Prevention demonstrate that patients with cardiovascular comorbidities have a much higher mortality (10.5% vs 0.9%).18 The background clinical profile of patients with acute myocardial injury may also facilitate direct virus-mediated cardiotoxicity or secondary myocardial involvement in a systemic inflammatory response. Increased prevalence of pre-existing cardiovascular disease is also likely to explain the more frequent

Table 2  Variables related to the value of hs-TnT

<table>
<thead>
<tr>
<th></th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B (SE)</td>
<td>P value</td>
</tr>
<tr>
<td>Age</td>
<td>0.030 (0.006)</td>
<td>0.000</td>
</tr>
<tr>
<td>Males</td>
<td>−0.090 (0.260)</td>
<td>0.730</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.116 (0.446)</td>
<td>0.794</td>
</tr>
<tr>
<td>Use of ACEi/ARB</td>
<td>2.584 (0.479)</td>
<td>0.000</td>
</tr>
<tr>
<td>Use of CCB</td>
<td>1.066 (0.370)</td>
<td>0.005</td>
</tr>
<tr>
<td>WBC</td>
<td>−0.001 (0.046)</td>
<td>0.976</td>
</tr>
<tr>
<td>eGFR</td>
<td>−0.018 (0.003)</td>
<td>0.000</td>
</tr>
<tr>
<td>CRP</td>
<td>0.018 (0.004)</td>
<td>0.000</td>
</tr>
<tr>
<td>Pulmonary lesion ratio</td>
<td>0.036 (0.006)</td>
<td>0.000</td>
</tr>
<tr>
<td>Oxygenation index</td>
<td>−0.005 (0.001)</td>
<td>0.000</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.561 (0.345)</td>
<td>0.108</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>1.730 (0.521)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.444 (0.265)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>1.199 (0.492)</td>
<td>0.017</td>
</tr>
</tbody>
</table>

ACEi, ACE inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; CRP, C reactive protein; eGFR, estimated glomerular filtration rate; hs-TnT, high-sensitivity troponin T; WBC, white blood cell count.

Figure 2  Correlation between ejection fraction and log hs-TnT (n=32). hs-TnT, high-sensitivity troponin T.

Table 3  In-hospital clinical outcomes

<table>
<thead>
<tr>
<th></th>
<th>Total (N=101)</th>
<th>hs-TnT≤14 pg/mL (n=85)</th>
<th>hs-TnT&gt;14 pg/mL (n=16)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death, n (%)</td>
<td>3 (3.0)</td>
<td>0</td>
<td>3 (18.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Severe case, n (%)</td>
<td>37 (36.6)</td>
<td>25 (29.4)</td>
<td>12 (75)</td>
<td>0.001</td>
</tr>
<tr>
<td>Admission to ICU, n (%)</td>
<td>31 (30.7)</td>
<td>21 (24.7)</td>
<td>10 (62.5)</td>
<td>0.003</td>
</tr>
<tr>
<td>Mechanical ventilation, n (%)</td>
<td>11 (10.9)</td>
<td>4 (4.7)</td>
<td>7 (43.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vasoactive agents, n (%)</td>
<td>5 (5.0)</td>
<td>0</td>
<td>5 (31.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICU duration, mean (SD)</td>
<td>3.26 (6.16)</td>
<td>2.86 (5.56)</td>
<td>5.38 (8.61)</td>
<td>0.135</td>
</tr>
</tbody>
</table>

ICU, intensive care unit.
use of ACEi/ARB in the group of patients with acute myocardial injury. ACE2 is the functional receptor for SARS-CoV-2, and increased levels associated with the use of renin–angiotensin–aldosterone system inhibitors might increase the possibility of virus-mediated myocardial damage. However, this explanation remains hypothetical, and there are no current reliable data to justify alteration of ACEi/ARB treatment in patients with COVID-19.

Hubei Province (Wuhan) has an over 100-fold greater number of COVID-19 cases than Sichuan Province. The surge of cases needing medical care, especially in the early period of this outbreak, posed a major challenge to the regional healthcare system. Our results further support the association of cardiac injury with adverse events in patients with COVID-19. Furthermore, the disparity in the number of cases between the adjacent regions of Hubei and Sichuan Provinces clearly demonstrates the public health advantages of ‘lockdown’ in the national and international management of the COVID-19 outbreak.

Our study has inevitable limitations at this early stage of the COVID-19 outbreak. With a small sample size, we are unable to draw definitive conclusions and acknowledge the existence of selection bias during this very early study period in specialist hub centres. Owing to circumstances, complete documentation of exposure history and laboratory testing was not available for every patient, and echocardiography was only performed for clinical expediency. As a consequence, we were only able to define acute myocardial injury by troponin elevation without detailing myocardial tissue characteristics and haemodynamic function. Caution should be taken when interpreting the multivariable analysis of hs-TnT since the model is likely underpowered to assess independent associations for other predictors in the model.

CONCLUSIONS

Acute myocardial injury, as indicated by troponin elevation, is common in patients with COVID-19, particularly in the elderly with pre-existing cardiovascular comorbidities, and is associated with increased risk of progressive severe disease, need for ICU admission, mechanical ventilation and use of vasoactive agents, and death. Targeted treatment and preventative strategies are urgently needed for this vulnerable patient group.
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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval The study was approved by the institutional ethics committee (study number 2020–226) and all patients provided written informed consent.

Provenance and peer review Not commissioned; internally peer reviewed.

Data availability statement Data are available upon reasonable request. The datasets used during the current study are available from the corresponding author on reasonable request. Individual participant data without names and identifiers that underlie the result reported in this article are available on request. The data will be available for others to request immediately after publication of the article. The proposal with detailed description of study objectives will be needed for evaluation of the reasonability to request our data. The data requestors will need to sign a data access agreement to gain the datasets. The proposals should be directed to hmiaochen@vip.sina.com.

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